IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Magnali ROUQUIE
                       Nicolas CARITEY
                       Laurent GAUBERT

Serial No:

Filed:

For: A METHOD OF MODELING AND SIMULATING A BIOLOGICAL SYSTEM, AND
A MODEL FOR USE IN THE METHOD

DECLARATION

I, Andrew Scott Marland, of 11, rue de Florence, 75008 Paris, France, declare that I am well acquainted with the English and French languages and that the attached translation of the French language PCT international application, Serial No. **PCT/FR2004/002115** is a true and faithful translation of that document as filed.

All statements made herein are to my own knowledge true, and all statements made on information and belief are believed to be true; and further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any document or any registration resulting therefrom.

Date: March 2, 2006

Andrew Scott Marland

A METHOD OF MODELING AND SIMULATING A BIOLOGICAL SYSTEM,
AND A MODEL FOR USE IN THE METHOD

FIELD OF THE INVENTION

5   The present invention relates to methods of modeling
and simulating biological systems.

BACKGROUND OF THE INVENTION

Methods of this kind have been described by ROUX-
ROUQUIE et al. (R.C. Biologies 325 (2002) 419-430), for
10   example.

Prior art methods of modeling and simulating
biological systems have the drawback of being implemented
on an ad hoc basis and in a non-standardized manner, with
the result that they are incompatible with each other and
15   difficult to understand for biologists who are not
familiar with applied mathematics. They are therefore
difficult to validate and of uncertain reliability.

SUMMARY OF THE INVENTION

One particular object of the present invention is to
20   alleviate these drawbacks.

To this end, the invention proposes a method of
modeling and simulating a biological system comprising
one or more tangible biological functional entities
modeled by at least:

25   · a morphological occurrence comprising at least a
biochemical constituent that identifies the persistent
properties of the biological functional entity, and at
least a transformation representing the way in which the
constituent behaves as a function of the space-time
30   context;

· a spatial occurrence representing at least a
spatial characteristic of the biological functional
entity; and

· a temporal occurrence representing at least a
35   temporal characteristic of the biological functional
entity;

which method simulates the behavior of said biological

functional entities by recursively determining the effect on their functioning and on their behavior (their activities) of all changes affecting said occurrences, including transformations.

5   Thus the modeling and simulation method of the invention distinguishes between:

       · persistent characters (called "constituents" in the context of the invention) of the entities forming the biological system in question (name, category; for

10   example: a cell, a nucleus, a protein, *etc.*); and

       · functional states of those constituents that depend on the active morphological occurrence of the entities and the space-time context in which they are active.

15   By means of the above features, the biological system to be simulated is modeled explicitly, in a standardizable and logical manner that is readily accessible to a biologist who is not a specialist in mathematics or programming (in particular, a biologist

20   can readily verify the morphological characteristics and space-time characteristics, which are factual).

       Moreover, the method of the invention separates simulation, which uses diverse mathematical calculation methods, and modeling: thus it is possible to apply a

25   plurality of simulation methods to the same biological system model, either during successive simulations or simultaneously by applying a plurality of types of simulation to different portions of the biological system.

30   Various implementations of the method of the invention may have one or more of the following features, where appropriate:

       · the temporal occurrence is selected from an age of the biological functional entity and a period during

35   which that functional entity is active;

       · said biological constituent is selected from an organism, a tissue, a cell, an organite, and a molecule;

· said transformation is selected from a cellular transformation and a molecular transformation;

· said transformation is a molecular transformation selected from:

· a covalent molecular transformation, itself selected from a covalent transformation of proteins corresponding to a post-traductional transformation or a co-traductional transformation (such as a phosphorylation or a dephosphorylation), a covalent RNA transformation corresponding to RNA synthesis or maturation, and a covalent DNA transformation corresponding to DNA synthesis, damage or repair; and

· a non-covalent transformation, itself selected from a hydrophobic transformation, a transformation caused by Van der Waals forces, electrostatic forces or attraction between an electronegative atom of one molecule and a hydrogen atom of another molecule, and a steric transformation caused by attraction between adjacent atoms;

· some of said function biological entities are included in a higher biological functional entity;

· at least some of said biological functional entities include lower biological functional entities;

· some functional entities constitute the environment of at least some other functional entities with which they interact;

· the biological system further comprises intangible biological functional entities modeled by temporal occurrences and where appropriate by spatial and morphological occurrences;

· said intangible biological functional entities comprise biochemical reactions.

Furthermore, the invention also consists in a model intended in particular (but not exclusively) for implementing a method as defined above, the model comprising one or more tangible biological functional entities modeled by at least:

· a morphological occurrence comprising at least a biochemical constituent that identifies the biological functional entity, and at least a transformation representing the way in which that constituent behaves as

5 a function of the space-time context;

· a spatial occurrence representing at least a spatial characteristic of the biological functional entity; and

· a temporal occurrence representing at least a

10 temporal characteristic of the biological functional entity.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

Other features and advantages of the invention become apparent in the course of the description below of

15 an implementation of the invention given by way of non-limiting example.

The invention proposes a metamodel that is particularly suitable for modeling biological systems, in particular with a view to simulation for estimating their

20 behavior.

According to the invention, the biological system is modeled as a set of tangible or intangible biological functional entities.

Each tangible biological functional entity is

25 modeled by at least:

· a morphological occurrence including a biochemical constituent that identifies the biological functional entity and a transformation representing the way in which that constituent behaves as a function of the space-time

30 context;

· a spatial occurrence representing a spatial characteristic of the biological functional entity (in particular the age of that entity and/or a period of activity of that entity); and

35 · a temporal occurrence representing a temporal characteristic of the biological functional entity (corresponding to the position of the biological

functional entity relative to its external environment), for example.

Where appropriate, each tangible biological functional entity may be included in a higher biological functional entity and/or may itself include lower biological functional entities. Moreover, at least some functional entities may constitute the environment of at least some other functional entities with which they interact.

The biochemical constituents referred to above may comprise, for example:

· a living organism;

· a biological tissue;

· a cell, for example an epithelial cell or a lymphocyte cell;

· an organite, for example a nucleus or a ribosome; and

· a molecule, for example an RNA molecule, a DNA element (for example a gene, a regulator element or a promoter), or a protein.

The transformations mentioned above may include cellular transformations and molecular transformations, for example.

The molecular transformations in question may comprise, for example:

· covalent transformations of proteins (in particular post-traductional transformations, such as phosphorylation or dephosphorylation, and co-traductional transformations), covalent RNA transformations (in particular synthesis and splicing), and covalent DNA transformations (in particular synthesis, damage and repair by base excision, recombination, excision of nucleotides, photoreactivation and repairing matches); and

· non-covalent hydrophobic molecular transformations, or transformations arising from Van der Waals forces, electrostatic forces or attraction between

an electronegative atom of one molecule and an hydrogen
atom of another molecule, or steric transformations
caused by attraction between adjacent atoms (in
particular phospho-isomerization).

5   Moreover, at least some of the biological functional
entities modeling the biological system may be intangible
biological functional entities, in particular biochemical
reactions.

These intangible biological functional entities need
10   not include morphological occurrences, in which case they
include only temporal occurrences and where applicable
spatial occurrences.

The biological system referred to above may be
modeled in particular using the UML™ language and modeled
15   functional units such as UML™ active objects, which
facilitates mapping to formal languages facilitating
analysis and simulation, for example the Pi Calculus
language.

The status of each biological functional entity is
20   defined at all times by the time and space values of
these morphological occurrences and the behavior of the
biological system over time is represented by the
trajectory of the states of each biological functional
entity in the frame of reference (shape, time, space).

25   To determine this behavior, the behavior of the
biological functional entities over time is simulated
recursively, progressively determining if at least some
of the morphological transformations of said biological
functional entities are produced as a function of the
30   space-time context, as and when the biological functional
entities interact.

Thus carrying out an action, for example a
transformation, changes the value of the shape occurrence
and changes the state of the functional entity, which
35   then effects a transition, for example from the inactive
state to the active state; the production of this new
state constitutes an event that can trigger another

action, for example transfer of the functional entity from one cellular compartment to another by modifying the spatial occurrence value.

The metamodel of the invention may be used to model
5 and simulate, for example:

· biochemical reactions, in which case the morphological occurrences of the biological functional entities (for example enzymes) comprise the biochemical compounds that are the subject of these reactions; to
10 simulate the behavior of populations of functional entities (for example enzymes), the "population" functional entities may comprise concentrations of the constituents, for example, the reactions to be simulated then being modeled in a "protocol" file or by the
15 morphological characteristics of a higher biological functional entity, and the simulation being effected by solving differential equations, for example, as in the "E-cell" software, or by a stochastic algorithm, as in the "Stochsim" software;
20 · any biological process, for example using the prior art "Genomic Object Net" simulation software.